Synthesis of Fluorinated Analogues of Myristic Acid as Potential Inhibitors of Egyptian Armyworm (*Spodoptera littoralis*) Δ^{11} Desaturase

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FOOTNOTES

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Abreviations: DAST, diethylaminosulfur trifluoride; DEPT, distortionless enhancement by polarization transfer; DMSO, dimethyl sulfoxide; GC/MS, gas chomatography/mass spectrometry; IR, infrared spectroscopy; MTBE, *tert*-butyl methyl ether; NMR, nuclear magnetic resonance; NBS, *N*-bromosuccinimide; S. D. standard deviation; SIM, selected ion monitoring; THF, tetrahydrofuran; TLC, thin-layer chromatography; UV, Ultraviolet.

ABSTRACT

In order to study the activity of the different desaturases present in the pheromone biosynthetic pathway of the Egyptian armyworm, *Spodoptera littoralis,* we report the preparation, characterization and the desaturase inhibition of a series of mono- and *gem*-difluorinated analogues of myristic acid with halogen substitution at C8-C11 positions of the aliphatic chain *via* specifically positioned dithiane precursors. Thus, transformation of dithianes by treatment with NBS in presence of H_2O followed by reduction with $LiAlH_4$ afforded the appropriate alcohols which reacted with diethylaminosulfur trifluoride (DAST) to give rise to the corresponding monofluoroderivative intermediates. Alternatively, the introduction of the *gem*-difluoro functionality was carried out by reaction of the appropriate dithiane intermediate with 1,3-dibromo-5,5-dimethylhydantoin in presence of HF/pyridine. The activity of these fluorinated fatty acids as substrates and inhibitors of the desaturases involved in the biosynthesis of the sex pheromonal blend of *Spodoptera littoralis* has been studied. In this case, 11-fluorotetradecanoic acid elicited a moderate inhibitory activity in front of Δ^{11} desaturase.

INTRODUCTION

Biosynthesis of unsaturated fatty acids in living organisms occurs by the direct introduction of double bonds into a saturated precursor in a remarkable reaction that is catalyzed by specific desaturases. Furthermore, in insects, some moth pheromone glands contain additional desaturases that transform unsaturated fatty acids to conjugated dienoic acids. In order to gain insight into general aspects of desaturase enzyme catalysis mechanism, studies on the activity of the above mentioned enzymes are also desirable. In this context, we have recently demonstrated some important features on that desaturation mechanism of the fatty acid dienoic functionality of the Egyptian armyworm, *Spodoptera littoralis,* sex pheromone blend by studying the stereochemistry (1-3) and cryptoregiochemistry (4,5) of the desaturation process. However, our ongoing interest in the above desaturases has led us to undertake the search for specific enzyme inhibitors that could be useful in such studies. In this sense, replacement of hydrogen by fluorine in those positions of the aliphatic chain closer to the interaction with the enzyme active center of Δ^{11} and Δ^{9} desaturases might be effective. Previous work of our laboratory has shown that different mono-and difluoropalmitic acids can inhibit the β-oxidation step of the biosynthesis of (*Z*,*E*)-9,11-tetradecadienyl acetate, the major component of *S. littoralis* sex pheromone blend (6-9). In insect sex pheromone we (10-12) and others (13,14) demonstrated that replacements of hydrogen atom(s) by fluorine mimic, potentiate or inhibit the action of the natural products.

Recently, Behrouzian et al. (15,16) have studied the desaturation of both enantiomers of 9-fluoroderivatives of stearic acids by stearoyl acyl carrier protein Δ^{9} desaturase isolated from castor seed oil in which valuable new insights into the enantioselectivity of this enzyme in the dehydrogenation and oxidation reactions were obtained. In our

case, we were interested in studying the activity of those mono- and *gem*-difluoroderivatives of myristic acids bearing the fluorine substitution at C8-C11 positions. For this it was required to develope a versatile synthetic route which could also eventually be adapted to the preparation of the corresponding enantiomeric monofluorinated derivatives.

In the present communication we report on this synthetic route and on the preliminary results of the activity of the above fluorinated analogs with the Δ^{11} desaturase of *S. littoralis*.

EXPERIMENTAL PROCEDURES

General Methods. Commercial grade reagents and solvents were directly used as supplied with the following excepcions: diethyl ether and THF were distilled over Na/benzophenone under argon atmosphere. Reactions sensitive to moisture and oxygen were carried out under argon or nitrogen atmosphere. Unless otherwise stated, organic solutions obtained from workup of crude reaction mixtures were dried over anhydrous $MgSO_4$, purification procedures were carried out by flash chromatography on silica gel (230-400 mesh) and products were mostly obtained as oils and they were at least 98% pure (GC). Visualization of UV-inactive materials was accomplished by soaking the TLC plates in a ethanolic solution of anisaldehyd and sulfuric acid (v/v/v, 96:2:2) or in an ethanolic solution of phosphomolybdic acid (5%).

All ^{1}H NMR spectra were acquired at 300 MHz, and ^{13}C NMR spectra, at 75 MHz in $CDCl_3$ solutions, and chemical shifts are given in ppm downfield from $Si(CH_3)_4$ for ^{1}H, and $CDCl_3$ for ^{13}C. In the same way, ^{19}F NMR spectra were acquired at 282 MHz and are reported in ppm downfield from $CFCl_3$. Assignment of critical signals in the ^{13}C NMR spectra was carried out on the basis of distortionless enhancement by polarization

transfer (DEPT). GC/MS was performed by electron impact at 20 eV using the equipment and conditions described below. All IR spectra were run on a Michelson Bomem MB-120 spectrometer. Elemental analysis were obtained in the Microanalysis Service of IIQAB-CSIC.

***In Vitro* Gland Culture Procedure**. Inhibition of Δ^{11} desaturase activity by the fluorinated derivatives synthesized was also investigated using $d_3$tetradecanoic acid as substrate and determining the amounts of d_3(*E*)-11-tetradecenoic acic formed in controls and experimental glands. These experiments were carried out using round-bottom-96 well plates. To each well, a 10 μL drop of incubation medium was added. The incubation medium consisted of the commercial Grace´s insect medium (17) (135 μL) and a DMSO solution (15 μL) of a 1:1:1 mixture of $d_3$16:acid/$d_3$14:acid/fluoroacid (10 mg/mL each) for treated tissues or a dimethyl sulfoxide solution of $d_3$14:Acid (10 mg/mL) for controls. One-day-old virgin *S. littoralis* females were briefly anesthetized on ice and the pheromone glands were excised, carefully cleaned and immersed individually into a drop of the incubation medium. Plates were sealed with adherent plastic covers and incubations proceeded for 3 h at 25 ºC. After this time, to obtain the methyl ester derivatives of the gland lipids for analysis, pheromone glands were collected and soaked in 0.5 M KOH for 30 min, and then the organic solution was neutralized with 1 N HCl and extracted with hexane containing methyl pentadecanoate (10 ng/gland) as internal standard for quantification. Five glands were used for each sample.

Instrumental Analysis of the Biological Extracts. The extracts were analyzed by gas chromatography-coupled to mass spectrometry (GC-MS), at 70 eV, on a Fisons gas chromatograph (8000 series) coupled to a Fisons MD-800 mass selective detector. The system was equipped with a non-polar Hewlett Packard HP-1 capillary column (30 m x

0.20 mm I.D) using the following program: from 120 ºC to 180 ºC at 5 ºC/min and then 260 ºC at 2 ºC/min after an initial delay of 2 min. Analyses were carried out under selected ion monitoring (SIM) mode. Selected ions were 245 (trideuterated methyl tetradecanoate, $M^{\bullet +}$), 242 (methyl tetradecanoate, $M^{\bullet +}$), 243 (trideuterated methyl (*Z*)-11 and (*E*)-11 tetradecenoates, $M^{\bullet +}$), 240 (methyl (*Z*)-11 and (*E*)-11 tetradecenoates, $M^{\bullet +}$). To investigate the conversion of the fluorofatty acids into their unsaturated derivatives, the analyses of the corresponding methyl esters were carried out under the full scan method.

Preparation of products 4a-d, 5a-d and **6a-d** were carried out according to previously described procedures (4,18).

Synthesis of dithianes 7a-d. General Procedure. These products were obtained following the procedure reported by Seebach et al. (19). To a solution of the dithiane **6** (10 mmol) in 15 mL of dry THF and kept at -20 ºC was added 12 mmol of an hexane BuLi solution (7.5 mL, 1.6M). The pale colored reaction mixture was stirred for 30 min, cooled at -78 ºC and kept for 10 min and then product **5** (8 mmol) was added dropwise and stirring was continued at -78 ºC for 2 h. The resulting solution was allowed to warm to room temperature and the solvent was then evaporated. The residue was suspended in 50 mL of H_2O, extracted with CH_2Cl_2, dried and concentrated to dryness. The residue was purified by flash chromatography on silica gel using a gradient of 0-10% MTBE in hexane to give the pure dithiane **7** in 74-80% yields.

2-Propyl-2-(11,13-dioxatetradecyl)-1,3-dithiane (7a). (2.15 g, 74% yield); IR 2930, 2855, 1465, 1275, 1150, 1110, 1045, 920 cm^{-1}; ^1H NMR δ 4.62 (s, 2H, OCH_2O), 3.52 (t, J = 6.5 Hz, 2H, CH_2O), 3.36 (s, 3H, OCH_3), 2.81 (4H, SCH_2), 2.02-1.90 (2H, CH_2CH_2S), 1.90-1.80 (4H, $SSCCH_2$), 1.66-1.50 (2H, CH_2CH_2O), 1.50-1.40 (2H, CH_2CH_3), 1.42-1.23 (14H, CH_2), 0.94 (t, J = 7 Hz, 3H, CH_3); ^{13}C NMR δ 96.3

(OCH_2O), 67.8 (CH_2O), 55.0 (OCH_3), 53.3 (CSS), 40.4 (*CH_2*CSS), 38.2 (*CH_2*CSS), 29.8 (CH_2S), 29.7 (CH_2S), 29.5 (CH_2), 29.5(CH_2), 29.4 (CH_2), 29.4 (CH_2), 26.2 (CH_2), 26.0 (CH_2), 25.6 (CH_2), 24.0 (CH_2), 17.4 (*CH_2*CH_3), 14.3 (CH_3); MS *m/z* 362 ($M^{\cdot +}$, 15), 319 (20), 287 (15), 161 (100); Anal. Calcd for $C_{19}H_{38}O_2S_2$: C, 62.93; H, 10.56; S, 17.68. Found: C, 62.84; H, 10.47; S, 17.56.

Synthesis of ketones 8a-d from dithianes 7a-d. General procedure. To a solution of NBS (5.45 g, 30 mmol) in 47 mL of acetone and 2.5 mL of H_2O kept at -30 ºC was added dropwise 1.81 g of dithiane **7** (5 mmol) dissolved in 50 mL of the same solvent mixture. Stirring was continued for 5 min and a 10% $Na_2S_2O_3$ water solution was added until the orange colour of the solution disappeared. The solvent was evaporated at reduced pressure, the residue extracted with CH_2Cl_2, dried and concentrated to dryness. The residue was purified by flash chromatography on silica gel using a gradient of 0-10% MTBE in hexane to give the pure ketones in 87-92% yields.

15,17-Dioxa-4-octadecanone (8a). (1.25 g, 92% yield); IR 2930, 2855, 1715 (CO), 1465, 1410, 1370, 1150, 1110, 1045, 920 cm^{-1}; ^1H NMR δ 4.62 (s, 2H, OCH_2O), 3.51 (t, *J* = 6.5 Hz, 2H, CH_2O), 3.36 (s, 3H, OCH_3), 2.38 (t, *J* = 7.5 Hz, 4H, CH_2CO), 1.67-1.46 (6H, *CH_2*CH_2CO and *CH_2*CH_2O), 1.40-1.18 (12H, CH_2), 0.91 (t, *J* = 7.5 Hz, 3H, CH_3) ^{13}C NMR δ 211.6 (CO), 96.3 (OCH_2O), 67.8 (CH_2O), 55.0 (OCH_3), 44.7 (CH_2), 42.8 (CH_2), 29.7 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.2 (CH_2), 26.2 (CH_2), 23.8 (CH_2), 17.3 (CH_2), 13.7 (CH_3); MS *m/z* 257 ($M^{\cdot +}$-CH_3, 1), 241 (2), 227 (5), 167 (10), 149 (15), 99 (20), 83 (35), 71 (100), 69 (40), 55 (45); Anal. Calcd for $C_{16}H_{32}O_3$: C, 70.54; H, 11.84. Found: C, 70.60; H, 11.68.

Preparation of alcohols 9a-d from ketones 8a-d. **General Procedure**. A solution of the corresponding ketone **8** in Et_2O, maintained under argon and at room temperature, was treated with 4 molar equiv of $LiAlH_4$, and the mixture was stirred until the reaction

was completed. Reagent excess was carefully quenched with water and after the usual work up, the residue obtained was purified by flash chromatography on silica gel using hexane/MTBE 80:20 to give the corresponding pure alcohols **9** in 92-96% yields.

15,17-Dioxa-4-octadecanol (9a). This alcohol was isolated (1.05 g, 96% yield) starting from 1.09 g (4 mmol) of ketone **8a**. IR 3450 (OH), 2930, 2855, 1465, 1385, 1215, 1150, 1110, 1045, 920 cm $^{-1}$; ^{1}H NMR δ 4.61 (s, 2H, OCH_2O), 3.59 (bs, 1H, OH), 3.51 (t, *J* = 6.5 Hz, 2H, CH_2O), 3.36 (s, 3H, OCH_3), 1.59 (m, 2H, CH_2CH_2O), 1.52-1.22 (21H), 0.92 (t, *J* = 6.5 Hz, 3H, CH_3) ^{13}C NMR δ 96.3 (OCH_2O), 71.7 (CHOH), 67.8 (CH_2O), 55.0 (OCH_3), 39.6 (CH_2), 37.5 (CH_2), 29.7 (CH_2), 29.7 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.4 (CH_2), 26.2 (CH_2), 25.6 (CH_2), 18.8 (CH_2), 14.1 (CH_3); MS *m/z* 225 ($M^{\cdot +}$-H_2O-OCH_3, 1), 200 (10), 169 (5), 149 (12), 109 (15), 95 (35), 81 (25), 69 (30), 55 (60), 45 (100); Anal. Calcd for $C_{16}H_{34}O_3$: C, 70.02; H, 12.49. Found: C, 69.94; H, 12.35.

Preparation of monofluoride derivatives 10a-d. General procedure. To a stirred solution of the corresponding alcohol **9** in 2 ml of dry CH_2Cl_2 at –78 ºC DAST was added dropwise (1.15 equiv.) with a syringe under nitrogen atmosphere. Stirring was continued for 2 h and then the reaction mixture was allowed to warm to room temperature and carefully poured over a cold sat $NaHCO_3$ solution. The mixture was extracted with hexane and the organic layer was washed with brine, dried, and concentrated to obtain a residue which was purified by flash chromatography on silica gel using a hexane/MTBE gradient (0-8%) to give the corresponding pure fluoroderivatives in 72-76% yields.

15,17-Dioxa-4-fluorooctadecane (10a). This product was isolated (207 mg, 75% yield) starting from 274 mg (1 mmol) of alcohol **9a**. IR 2930, 2855, 1465, 1385, 1150, 1110, 1045, 920 cm $^{-1}$; ^{1}H NMR δ 4.62 (s, 2H, OCH_2O), 4.47 (dm, J_1 = 49.5 Hz, 1H, CHF),

3.52 (t, J = 6.5 Hz, 2H, CH_2O), 3.36 (s, 3H, OCH_3), 1.72-1.22 (22H, CH_2), 0.93 (t, J = 7 Hz, 3H, CH_3) ^{13}C NMR δ 96.4 (OCH_2O), 94.3 (d, J = 166.5 Hz, CHF), 67.8 (CH_2O), 55.1 (OCH_3), 35.1 (d, J = 20.5 Hz, CH_2CHF), 34.8 (d, J = 21 Hz, CH_2CHF), 29.7 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.4 (CH_2), 26.2 (CH_2), 25.1 (d, J = 4.5 Hz, CH_2), 18.4 (d, J = 4.5 Hz, CH_2CH_3), 14.0 (CH_3) ^{19}F NMR δ −180.8; MS *m/z* 275 ($M^{\cdot +}$-1, 1), 256 (1), 224 (5), 211 (8), 165 (15), 151 (10), 137 (22), 123 (40), 111 (60), 109 (65), 95 (90), 82 (100), 69 (85), 55 (70); Anal. Calcd for $C_{16}H_{33}FO_2$: C, 69.52; H, 12.03; F, 6.87. Found: C, 69.60; H, 11.86; F, 6.69.

Synthesis of *gem*-difluoro derivatives 11a-d from dithianes 7a-d. General procedure. These reactions were performed according to the procedure developped by Sondej and Katzenellenbogen (20). 1,3-Dibromo-5,5-dimethylhydantoin was dissolved in 12 ml of dry CH_2Cl_2 and stirred under nitrogen. The mixture was cooled at –90 ºC and 0.5 ml of pyridinium poly (hydrogen fluoride) was added via a plastic syringe, followed by the dropwise addition of the corresponding dithiane (1 mmol). Reaction was stirred overnight at –78 ºC, then poured over 10 ml of hexane, quenched with 10 ml of a sat. $NaHCO_3$ solution and extracted with hexane (2x10 ml). The organic fractions were combined, dried and concentrated. Residue was purified by flash chromatography on silica gel using a hexane/MTBE gradient (0-4%) to give the corresponding *gem*-difluoro derivatives in 55-65% yields).

15,17-Dioxa-4,4-difluorooctadecane (11a). This product was isolated (160 mg, 55% yield) starting from 362 mg (1 mmol) of dithiane **7a**. IR 2930, 2855, 1470, 1385, 1150, 1110, 1045, 920 cm^{-1}; ^1H NMR δ 4.62 (s, 2H, OCH_2O), 3.52 (t, J = 6.5 Hz, 2H, CH_2O), 3.36 (s, 3H, OCH_3), 1.92-1.67 (4H, CH_2CF_2), 1.66-1.39 (6H, $CH_2CH_2CF_2$ and CH_2CH_2O), 1.40-1.20 (12H), 0.96 (t, J = 7 Hz, 3H, CH_3) ^{13}C NMR δ 125.4 (t, J = 240 Hz, CF_2), 96.4 (OCH_2O), 67.8 (CH_2O), 55.1 (OCH_3), 38.3 (t, J = 25.5 Hz, CH_2CF_2),

36.3 (t, J = 25.5 Hz, CH_2CF_2), 29.7 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 26.2 (CH_2), 22.3 (t, J = 4.5 Hz, $CH_2CH_2CF_2$), 15.8 (t, J = 5 Hz, CH_2CH_3), 14.0 (CH_3) ^{19}F NMR δ –98.12 (quint, J = 16.5 Hz); MS *m/z* 244 ($M^{\cdot +}$-F-OCH_3, 2), 230 (4), 209 (4), 202 (3), 163 (15), 149 (20), 135 (25), 123 (40), 109 (44), 95 (50), 82 (100), 75 (80), 69 (75), 55 (96); Anal. Calcd for $C_{16}H_{32}F_2O_2$: C, 65.27; H, 10.95; F, 12.91. Found: C, 65.19; H, 10.84; F, 12.71.

Methoxymethane deprotection to alcohols 12a-d and 13a-d. General Procedure Products were deprotected to the corresponding alcohols by treatment with a MeOH/HCl solution (0.5M) for 24 h at room temperature. Solvent was evaporated and the crude was treated with 2 ml of water, extracted with CH_2Cl_2, dried, and concentrated to a residue which was purified by flash cromatography on silica gel using a hexane/AcOEt gradient (0-10%) to give the corresponding pure alcohol derivatives in 85-95% yields).

11-fluoro-1-tetradecanol (12a). This alcohol was isolated (40 mg, 87% yield) from 55 mg (0.2 mmol) of the protected alcohol. IR 3305 (OH), 2920, 2850, 1470, 1065 cm $^{-1}$; ^{1}H NMR δ 4.47 (dm, J_1 = 49.5 Hz, 1H, CHF), 3.64 (t, J = 6.5 Hz, 2H, CH_2OH), 1.72-1.22 (22H, CH_2), 0.93 (t, J = 7 Hz, 3H, CH_3) ^{13}C NMR δ 94.3 (d, J = 166.0 Hz, CHF), 63.1 (CH_2OH), 37.1 (d, J = 21.0 Hz, CH_2CHF), 35.2 (d, J = 21 Hz, CH_2CHF), 32.8 (CH_2), 29.5 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 25.7 (CH_2), 25.1 (d, J = 4.5 Hz, CH_2CH_2CHF), 18.4 (d, J = 4.5 Hz, CH_2CH_3), 14.0 (CH_3) ^{19}F NMR δ –180.8; MS *m/z* 194 ($M^{\cdot +}$-F-H_2O-1, 2), 166 (5), 151 (5), 139 (15), 123 (20), 109 (35), 96 (65), 82 (100), 81 (70), 68 (60), 55 (70).

11,11-Difluoro-1-tetradecanol (13a). This alcohol was isolated (42 mg, 86% yield) from 59 mg (0.2 mmol) of the protected alcohol. IR 3330 (OH), 2930, 2850, 1460, 1210, 1180 cm $^{-1}$; ^{1}H NMR δ 3.63 (t, J = 6.5 Hz, 2H, CH_2OH), 1.90-1.67 (4H, CH_2CF_2),

1.66-1.39 (6H, $CH_2CH_2CF_2$ and CH_2CH_2-O), 1.40-1.20 (12H), 0.95 (t, J = 7 Hz, 3H, CH_3) ^{13}C NMR δ 125.4 (t, J = 240 Hz, CF_2), 63.0 (CH_2OH), 38.3 (t, J = 25.5 Hz, CH_2CF_2), 36.3 (t, J = 25.5 Hz, CH_2CF_2), 29.5 (CH_2), 29.4 (CH_2), 25.7 (CH_2), 22.3 (t, J = 4.5 Hz, $CH_2CH_2CF_2$), 15.8 (t, J = 5 Hz, CH_2CH_3), 13.9 (CH_3) ^{19}F NMR δ –98.11 (quint, J = 16.5 Hz); MS *m/z* 167 ($M^{\cdot +}$-2F-CH_2CH_2OH, 3), 149 (10), 124 (12), 114 (20), 96 (25), 82 (65), 81 (35), 69 (50), 55 (100).

Preparation of carboxylic acids 1a-d and 2a-d. Alcohols were dissolved in a solution of 4 ml of acetone and 350 μL of H_2SO_4 at -5 ºC and then 350 mg of CrO_3 dissolved in 700 μL of water was added dropwise. The reaction mixture was stirred at -10 ºC for 1 hour and then allowed to warm to room temperature and stirred for 6 h. The reaction mixture was concentrated and 2 mL of HCl (1M) added, extracted with CH_2Cl_2, dried, and concentrated to a residue that was purified by flash chromatography on silica gel using hexane/MTBE 85:15 to give the corresponding acids in 60-68% yields.

11-Fluorotetradecanoic acid (1a). This acid was isolated (17 mg, 68% yield) from 23 mg (0.1 mmol) of the starting alcohol **12a**. IR 2930, 2850, 1700 (CO), 1465, 1295, 935 cm $^{-1}$; ^{1}H NMR δ 4.47 (dm, J_1 = 49.5 Hz, 1H, CHF), 2.35 (t, J = 7.5 Hz, 2H, CH_2CO), 1.76-1.22 (22H, CH_2), 0.93 (t, J = 7 Hz, 3H, CH_3) ^{13}C NMR δ 178.4 (CO), 94.3 (d, J = 166.0 Hz, CHF), 37.2 (d, J = 20.5 Hz, CH_2CHF), 35.1 (d, J = 21 Hz, CH_2CHF), 33.9 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 29.2 (CH_2), 29.0 (CH_2), 25.1 (d, J = 4.5 Hz, CH_2CH_2CHF), 24.6 (CH_2), 18.4 (d, J = 4.5 Hz, CH_2CH_3), 14.0 (CH_3) ^{19}F NMR δ –180.8; MS *m/z* (-OMe ester) 238 ($M^{\cdot +}$-F-CH_3O -2, 1), 206 (3), 189 (2), 164 (5), 150 (5), 123 (10), 109 (10), 95 (15), 87 (20), 82 (65), 74 (100), 69 (20), 55 (40); Anal. Calcd for $C_{14}H_{27}FO_2$: C, 68.25; H, 11.05; F, 7.71, Found: C, 68.18; H, 11.01; F, 7.69.

10-Fluorotetradecanoic acid (1b) This acid was isolated (15 mg, 60% yield) from 23 mg (0.1 mmol) of the starting alcohol **12b**. IR 2930, 2850, 1700 (CO), 1465, 1295, 935

cm $^{-1}$; ^{1}H NMR δ 4.46 (dm, J_1 = 49.0 Hz, 1H, CHF), 2.35 (t, J = 7.5 Hz, 2H, CH_2-CO), 1.72-1.52 (4H, CH_2CHF), 1.52-1.20 (18H, CH_2), 0.91 (t, J = 7 Hz, 3H, CH_3) ^{13}C NMR δ 179.8 (CO), 94.6 (d, J = 166.5 Hz, CHF), 35.1 (d, J = 21 Hz, CH_2CHF), 34.8 (d, J = 21 Hz, CH_2CHF), 33.9 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 29.1 (CH_2), 29.0 (CH_2), 27.3 (d, J = 4.5 Hz, CH_2CH_2CHF), 25.1 (d, J = 4.5 Hz, CH_2CH_2CHF), 24.6 (CH_2), 22.6 (CH_2CH_3), 14.0 (CH_3) ^{19}F NMR δ –180.5; MS *m/z* (-OMe ester) 240 ($M^{\cdot+}$-F^--CH_3O^-, 1), 208 (5), 190 (2), 166 (15), 124 (10), 111 (15), 97 (30), 87 (35), 83 (35), 74 (100), 69 (50), 55 (75); Anal. Calcd for $C_{14}H_{27}FO_2$: C, 68.25; H, 11.05; F, 7.71, Found: C, 68.28; H, 11.04; F, 7.60.

9-Fluorotetradecanoic acid (1c). This acid was isolated (15 mg, 60% yield) from 24 mg (0.1 mmol) of the starting alcohol **12c**. IR 2935, 2855, 1700 (CO), 1470, 1295, 940 cm $^{-1}$; ^{1}H NMR δ 4.46 (dm, J_1 = 49.0 Hz, 1H,CHF), 3.64 (t, J = 6.5 Hz, 2H, CH_2CO), 1.72-1.22 (22H, CH_2), 0.89 (t, J = 7 Hz, 3H, CH_3) ^{13}C NMR δ 180.0 (CO), 94.6 (d, J = 166.5 Hz, CHF), 35.1 (d, J = 21 Hz, CH_2CHF), 32.7 (CH_2), 31.7 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 25.7 (CH_2), 25.1 (d, J = 4.5 Hz, CH_2CH_2CHF), 24.8 (d, J = 4.5 Hz, CH_2CH_2CHF), 22.5 (CH_2), 14.0 (CH_3) ^{19}F NMR δ –180.5; MS *m/z* (-OMe ester) 240 ($M^{\cdot+}$-F-CH_3O, 1), 208 (2), 190 (2), 166 (15), 124 (10), 111 (15), 97 (30), 87 (35), 83 (35), 74 (100), 69 (50), 55 (40); Anal. Calcd for $C_{14}H_{27}FO_2$: C, 68.25; H, 11.05; F, 7.71, Found: C, 68.24; H, 11.00; F, 7.63.

8-Fluorotetradecanoic acid (1d). This acid was isolated (16 mg, 65% yield) from 24 mg (0.1 mmol) of the starting alcohol **12d**. IR 2930, 2850, 1700 (CO), 1465, 1295, 935 cm $^{-1}$; ^{1}H NMR δ 4.46 (dm, J_1 = 49.0 Hz, 1H, CHF), 3.64 (t, J = 6.5 Hz, 2H, CH_2CO), 1.74-1.20 (22H, CH_2), 0.89 (t, J = 7 Hz, 3H, CH_3) ^{13}C NMR δ 180.1 (CO), 94.6 (d, J = 166.5 Hz, CHF), 35.2 (d, J = 21 Hz, CH_2CHF), 35.1 (d, J = 21 Hz, CH_2CHF), 34.0 (CH_2), 31.7 (CH_2), 29.2 (CH_2), 29.1 (CH_2), 28.9 (CH_2), 25.1 (d, J = 4.5 Hz,

CH$_2$CH$_2$CHF), 25.0 (d, *J* = 4.5 Hz, *CH*$_2$CH$_2$CHF), 22.6 (*CH*$_2$CH$_3$), 14.1 (CH$_3$) ^{19}F NMR δ –180.5; MS *m/z* (-OMe ester) 238 (M·$^+$-F-CH$_3$O-2, 1), 206 (3), 189 (2), 164 (5), 150 (5), 123 (10), 109 (10), 95 (15), 87 (20), 82 (65), 74 (100), 55 (40); Anal. Calcd for $C_{14}H_{27}FO_2$: C, 68.25; H, 11.05; F, 7.71, Found: C, 68.13; H, 11.02; F, 7.55.

11,11-Difluorotetradecanoic acid (2a). This acid was isolated (10 mg, 63% yield) from 15 mg (0.06 mmol) of the starting alcohol **13a**. IR 2930, 2850, 1700 (CO), 1465, 1295, 935 cm $^{-1}$; ^{1}H NMR δ 3.63 (t, *J* = 6.5 Hz, 2H, CH$_2$CO), 1.90-1.67 (4H, CH$_2$CF$_2$), 1.66-1.39 (6H, *CH*$_2$CH$_2$CF$_2$ and *CH*$_2$CH$_2$CO), 1.40- 1.20 (12H, CH$_2$), 0.95 (t, *J* = 7 Hz, 3H, CH$_3$) ^{13}C NMR δ 179.8 (CO), 125.4 (t, *J* = 240 Hz, CF$_2$), 38.3 (t, *J* = 25.5 Hz, *CH*$_2$CF$_2$), 36.3 (t, *J* = 25.5 Hz, *CH*$_2$CF$_2$), 34.0 (CH$_2$), 29.4 (CH$_2$), 29.3 (CH$_2$), 29.2 (CH$_2$), 29.2 (CH$_2$), 29.0 (CH$_2$), 24.6 (CH$_2$), 22.3 (t, *J* = 4.5 Hz, *CH*$_2$CH$_2$CF$_2$), 15.8 (t, *J* = 5 Hz, *CH*$_2$CH$_3$), 14.0 (CH$_3$) ^{19}F NMR δ –98.11 (quint, *J* = 16.5 Hz); MS *m/z* (-OMe ester) 208 (M·$^+$-2F-CH$_3$-2, 5), 190 (2), 166 (15), 137 (10), 124 (20), 111 (20), 97 (30), 87 (35), 82 (35), 74 (100), 69 (50), 55 (70); Anal. Calcd for $C_{14}H_{26}F_2O_2$: C, 63.61; H, 9.91; F, 14.37, Found: C, 63.62; H, 9.79; F, 14.17.

10,10-Difluorotetradecanoic acid (2b). This acid was isolated (11 mg, 60% yield) from 18 mg (0.07 mmol) of the starting alcohol **13b**. IR 2930, 2850, 1700 (CO), 1465, 1295, 935 cm $^{-1}$; ^{1}H NMR δ 3.63 (t, *J* = 6.5 Hz, 2H, CH$_2$CO), 1.90-1.68 (4H, CH$_2$CF$_2$), 1.66-1.51 (2H, *CH*$_2$CH$_2$CO), 1.50- 1.20 (16H, CH$_2$), 0.92 (t, *J* = 7 Hz, 3H, CH$_3$) ^{13}C NMR δ 180.0 (CO), 125.5 (t, *J* = 240 Hz, CF$_2$), 36.2 (t, *J* = 25.5 Hz, *CH*$_2$CF$_2$), 36.0 (t, *J* = 25.5 Hz, *CH*$_2$CF$_2$), 34.0 (CH$_2$), 29.3 (CH$_2$), 29.2 (CH$_2$), 29.1 (CH$_2$), 29.0 (CH$_2$), 24.6 (CH$_2$), 24.4 (t, *J* = 4.5 Hz, *CH*$_2$CH$_2$CF$_2$), 22.5 (CH$_2$), 22.3 (t, *J* = 4.5 Hz, *CH*$_2$CH$_2$CF$_2$), 13.8 (CH$_3$) ^{19}F NMR δ –98.09 (quint, *J* = 16.5 Hz); MS *m/z* (-OMe ester) 238 (M·$^+$-2F-2, 2), 207 (1), 189 (2), 164 (10), 149 (10), 136 (10), 124 (10), 109 (15), 96 (75), 81 (30),

74 (100), 69 (20), 55 (50);Anal. Calcd for $C_{14}H_{26}F_2O_2$: C, 63.61; H, 9.91; F, 14.37, Found: C, 63.52; H, 9.78; F, 14.18.

9,9-Difluorotetradecanoic acid (2c). This acid was isolated (18 mg, 68% yield) from 25 mg (0.1 mmol) of the starting alcohol **13c**. IR 2930, 2850, 1700 (CO), 1465, 1295, 935 cm $^{-1}$; ^{1}H NMR δ 3.64 (t, *J* = 6.5 Hz, 2H, CH_2CO), 1.90-1.68 (4H, CH_2CF_2), 1.66-1.51 (4H, CH_2CH_2CO and $CH_2CH_2CF_2$), 1.52-1.40 (2H, $CH_2CH_2CF_2$), 1.50-1.20 (12H, CH_2), 0.90 (t, *J* = 7 Hz, 3H, CH_3) ^{13}C NMR δ 180.0 (CO), 125.4 (t, *J* = 240 Hz, CF_2), 36.3 (t, *J* = 25.5 Hz, CH_2CF_2), 36.2 (t, *J* = 25.5 Hz, CH_2CF_2), 34.0 (CH_2), 31.5 (CH_2), 29.2 (CH_2), 29.0 (CH_2), 28.8 (CH_2), 24.6 (CH_2), 22.4 (CH_2), 22.2 (t, *J* = 4.5 Hz, $CH_2CH_2CF_2$), 22.0 (t, *J* = 4.5 Hz, $CH_2CH_2CF_2$), 13.9 (CH_3) ^{19}F NMR δ –98.17 (quint, *J* = 16.5 Hz); MS *m/z* (-OMe ester) 238 ($M^{\cdot+}$-2F-2, 2), 207 (5), 196 (5), 164 (15), 150 (10), 135 (10), 110 (45), 95 (25), 87 (20), 81 (30), 74 (100), 69 (25), 55 (45);Anal. Calcd for $C_{14}H_{26}F_2O_2$: C, 63.61; H, 9.91; F, 14.37, Found: C, 63.59; H, 9.83; F, 14.18.

8,8-Difluorotetradecanoic acid (2d). This acid was isolated (10 mg, 63% yield) from 15 mg (0.06 mmol) of the starting alcohol **13d**. IR 2930, 2850, 1700 (CO), 1465, 1295, 935 cm $^{-1}$; ^{1}H NMR δ 3.64 (t, *J* = 6.5 Hz, 2H, CH_2CO), 1.90-1.68 (4H, CH_2CF_2), 1.68-1.51 (2H, CH_2CH_2CO), 1.50- 1.20 (16H, CH_2), 0.89 (t, *J* = 6.5 Hz, 3H, CH_3) ^{13}C NMR δ 180.0 (CO), 125.4 (t, *J* = 240 Hz, CF_2), 36.3 (t, *J* = 25.5 Hz, CH_2CF_2), 36.2 (t, *J* = 25.5 Hz, CH_2CF_2), 33.9 (CH_2), 31.6 (CH_2), 29.0 (CH_2), 29.0 (CH_2), 28.8 (CH_2), 24.4 (CH_2), 22.5 (CH_2), 22.2 (t, *J* = 4.5 Hz, $CH_2CH_2CF_2$), 22.1 (t, *J* = 4.5 Hz, $CH_2CH_2CF_2$), 14.0 (CH_3) ^{19}F NMR δ –98.13 (quint, *J* = 16.5 Hz); MS *m/z* (-OMe ester) 238 ($M^{\cdot+}$-2F-2, 2), 226 (5), 207 (5), 182 (10), 164 (15), 150 (10), 136 (10), 128 (15), 109 (15), 95 (25), 87 (15), 81 (25), 74 (100), 69 (25), 55 (35); Anal. Calcd for $C_{14}H_{26}F_2O_2$: C, 63.61; H, 9.91; F, 14.37, Found: C, 63.57; H, 9.75; F, 14.21.

RESULTS AND DISCUSION

Preparation and characterization of mono- and *gem*-difluoro myristic acids. The synthesis of myristic acids selectively substituted as mono- and *gem*-difluoro compounds at positions C8, C9, C10 and C11 was carried out as described in Scheme 1.

(Insert Scheme 1)

In this chemical pathway, properly functionalized dithianes **6** were used as myristic acid chain precursors. Thus, coupling of dithianes **6** with methoxymethane protected bromoderivatives **5** in presence of *n*-butyllitium afforded the corresponding dithianes **7** with the complete aliphatic chain. Recently, we used this kind of versatile intermediates for the preparation of mono- and double deuterated tridecanoic acids (18). In the same way, reaction of dithianes **7** with NBS in presence of water afforded ketones **8** and its reduction with $LiAlH_4$ afforded the corresponding alcohols **9** which eventually could be resolved to each one of the corresponding enantiomers (18). Because, our main goal was the synthesis of the different monofluoroderivatives as racemic mixtures, no procedures for their stereoselective formation were contemplated at this stage. Thus, introduction of a fluorine atom was achieved by displacement of the alcohol funtionality of **9** with DAST (21) using CH_2Cl_2 as solvent. Although, the yields of fluorination were acceptable olefinic side products were also detected as reported elsewhere (21,22). In the worst case, purification was achieved by flash chromatography on silica gel.

On the other hand, ketones are reported to be good substrates for the preparation of the *gem*-difluoro derivatives. But it was not possible to obtain the corresponding *gem*-difluoro derivatives when ketone **8** was treated with DAST or the mixture DAST/HF/pyridine using CH_2Cl_2 as solvent. Furthermore, we did not get any difluorinated product when reaction was carried out with CF_2Br_2 in presence of zinc (23). However, *gem*-difluoro compounds were prepared straightforward by reaction of

the previously obtained dithianes **7** with 1,3-dibromo-5,5-dimethylhydantoin in presence of HF/pyridine according to the procedure reported by Sondej and Katzenellenbogen (20). Methoxymethane deprotection of mono and *gem*-difluoro derivatives **10** and **11** to afford the alcohol intermediates **12** and **13**, respectively, was accomplished by acid treatment with HCl/MeOH (0.5M). Final Jones oxidation gave rise to the corresponding fluorinated fatty acids **1** and **2** with good yields. Characterization of the mono and difluorinated products were carried out by ^{1}H, ^{13}C and ^{19}F NMR.

Biochemical experiments

None of the compounds synthesized was converted by the Δ^{11}desaturase of the *S. littoralis* sex pheromone gland, as concluded from the careful examination of the GC/MS chromatograms corresponding to the methanolyzed lipidic extracts of the treated glands, which were identical to those of control tissues, to which no fluorofatty acid was administered. These results are in agreement with previously reported data using thiafatty acids (24). In that case, amongst 8-, 9-, 10-, 11-, 12- and 13-thiatetradecanoic acids, only the 13-thiaderivative was transformed into both (*Z*)- and (*E*)-11-thiatetradecenoic acids and (*E*)-11-thiatetradecenoic acid was further converted into (*Z*,*E*)-13-thia-9,11-tetradecadienoic acid. These overall results suggest that the substrate binding to moth Δ^{11}desaturases is very sensitive to heteroatom substitution, at least, at positions C8, C9, C10, C11 and C12, since replacement of methylene by the CH_2 bioisosteric sulfur or that of hydrogen by fluorine renders fatty acid analogs that are not desaturated at C11. In contrast, transformation of both thiafatty acids and fluorofatty acids by the yeast Δ^{9} desaturase has been reported by Behrouzian et al. (and references cited therein) (25).

As summarized in figure 1, only the 11-monofluoroderivative **1a** produced a moderate inhibition (50% at 1:1 substrate/inhibitor ratio). Since the assays were performed with racemic **1a**, it is reasonable to expect a higher inhibitory potency of the pure active enantiomer. This aspect is now under investigation in our laboratory.

(Insert figure 1)

The present work represents another example of the potential use of fluorinated compounds in biochemical studies of enzyme inhibition. The results obtained here confirm that there is not general rule that makes possible an easy prediction and that there is a dependence on the type and source of the enzyme studied.

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Figure 1

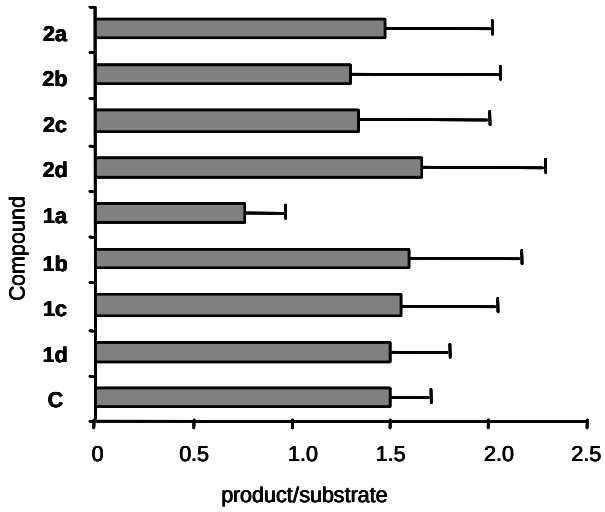
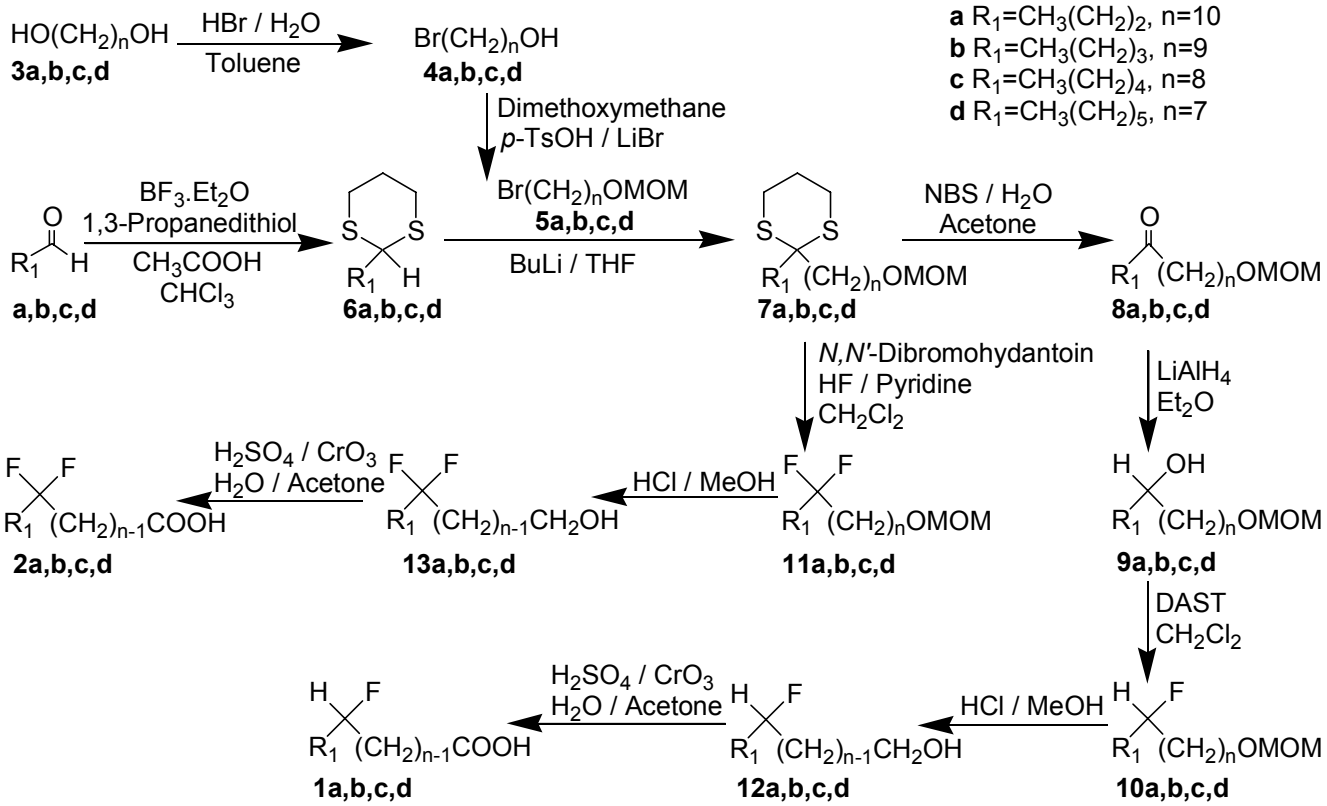


Figure 1. Effect of the fluorotetradecanoic acids **1a-d** and **2a-d** on the Δ^{11} desaturase of *S. littoralis.* Inhibition was determined on pheromone glands *in vitro* as described in the experimental section. The fatty acid methyl esters were analyzed by GC/MS and the ratios between the ions 243 (methyl d_3(*E*)-11-tetradecenoate, product) and 245 (methyl tetradecanoate, substrate) were calculated from their corresponding areas. Since the M^+ of methyl tetradecanoate is more abundant than that of methyl tetradecenoate, the values in figure 1 do not represent actual mass ratios between both compounds. Data correspond to the mean ± S.D. of five replicates). C, control.

Scheme 1


HO(CH2)nOH
3a,b,c,d
HBr / H2O
Toluene
Br(CH2)nOH
4a,b,c,d
Dimethoxymethane
p-TsOH / LiBr
Br(CH2)nOMOM
5a,b,c,d
BuLi / THF
BF3.Et2O
1,3-Propanedithiol
CH3COOH
CHCl3
a,b,c,d
6a,b,c,d
7a,b,c,d
NBS / H2O
Acetone
8a,b,c,d
N,N'-Dibromohydantoin
HF / Pyridine
CH2Cl2
LiAlH4
Et2O
9a,b,c,d
DAST
CH2Cl2
10a,b,c,d
HCl / MeOH
11a,b,c,d
12a,b,c,d
13a,b,c,d
H2SO4 / CrO3
H2O / Acetone
1a,b,c,d
2a,b,c,d
a R1=CH3(CH2)2, n=10
b R1=CH3(CH2)3, n=9
c R1=CH3(CH2)4, n=8
d R1=CH3(CH2)5, n=7